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TITLE: Inherited Susceptibility to Breast Cancer in Healthy  
Women: Mutation in Breast Cancer Genes, Immune  
Surveillance, and Psychological Distress

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2/29/2000  
Date

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#### INTRODUCTION:

Accumulating evidence indicates that modifying genes and/or environmental factors are likely to have a major impact on the expression of mutations in the recently identified breast cancer genes (BRCA1/BRCA2). The factors responsible for such differences in the penetrance of mutations in these primary susceptibility genes are not yet known. To date, speculation concerning these modifying factors has focused only on the usual suspects - hormonal/reproductive variables, which have already been shown in large scale epidemiological studies to be independent risk factors for the development of breast cancer independent of family history of the disease. Some risk factors for breast cancer, however, are likely to have an impact only in conjunction with mutations in primary susceptibility genes. Such factors, by themselves, might go undetected in standard epidemiological studies, but would become evident when examined in conjunction with testing for primary susceptibility genes. The purpose of the research supported by this IDEA grant award, is to provide the first critical test of possibility that variability in the strength of immune surveillance mechanisms against cancer (operationally defined as natural killer cell activity) may be a factor in determining the penetrance of mutations in breast cancer susceptibility genes. Two possible explanations for variability in NK cell activity are being investigated: 1) stress-induced immune suppression, and 2) inherited deficits in immune surveillance. In addition, we are examining the possibility that inherited deficits in immune surveillance may be independently associated with familial risk of breast cancer. The study "piggie-backs" on other ongoing studies involving genetic counseling and breast cancer gene testing at Mount Sinai Medical Center under the direction of Co-Investigator Eng and Co-Investigator Valdimarsdottir. The participants are recruited to three Study Groups (N=100/group) of comparable age for the research: 1) The Mutation-Positive Family History Group (Mut+Hist+) includes women whose family histories of cancer indicate a relative risk  $\geq 1.5$  for breast cancer and who carry a mutation in BRCA1 or BRCA2; 2) The Mutation-Negative Risk Family History Group (Mut-Hist+) includes women with comparable family histories, who do not carry mutations; 3) The Normal Risk Group (Mut-Hist-) includes women without family histories of cancer who are known not to carry mutations. Each participant is assessed on three separate occasions (at the same time of day): 1) immediately prior to notification of the results of their gene testing; 2) one month later; 2) three months later. Consistent with scheduling exigencies, one woman from each group is concurrently assessed, by personnel "blind" to group status. At each assessment, standardized self-report measures are completed, a blood sample (40 ml) is collected (as feasible), and \$23 reimbursement offered.

#### BODY:

Consistent with the Statement of Work, no results are yet available from this study. We have fallen substantially behind the proposed rate of study accrual for reasons related to a change in employment for Bovbjerg (PI) and Valdimarsdottir (co-invest.) which required a change in study site from Memorial Sloan-Kettering Cancer Center to The Mount Sinai Medical Center. The change in study site in turn required modification of collaborative arrangements (e.g., the addition of Eng as a co-investigator), set up of new facilities (e.g. Bovbjerg lab), hiring of new support staff, and additional attention to institutional review requirements. As a result of these considerations, no subjects have completed the entire set of proposed study

assessments, as of this annual review date. During this reporting period, however, the proposed psychological assessments of stress associated with familial risk and genetic testing have been conducted with 26 women, as a way for us to initiate the project prior to having the laboratory on line. Having now addressed the challenges posed by the transition to a new institution, with the laboratory now functional, with a backlog of potential participants for the study as a result of continuing research by our collaborators, and having husbanded our resources during this transition period for use later, we anticipate making strong progress during the next year.

**KEY RESEARCH ACCOMPLISHMENTS:**

At this point in the research, no results are yet available.

If results of the proposed research are consistent with the hypothesis that deficits in immune surveillance (e.g., as a result of stress) moderate the effects of mutations in primary susceptibility

**REPORTABLE OUTCOMES:**

National Cancer Institute	12/1/00 - 11/30/05	30%
(Valdimarsdottir)	\$347,596	
(Co-PI: Bovbjerg)		

BRCA Counseling/Testing for Urban African American Women

The purpose of the proposed research is to develop and test an enhanced genetic counseling program for African American women with strong family histories of breast cancer.

Overlap: If both pending grants are awarded, only one will be accepted.

National Cancer Institute (Aaronson)	12/1/00 - 11/30/05	20%
	\$1,661,954	

SPORE in Breast Cancer: Project 3: BRCA Counseling/Testing for Urban African American Women (Valdimarsdottir, PI)  
(Co-PI: Bovbjerg)

The purpose of the proposed research is to develop and test an enhanced genetic counseling program for African American women with strong family histories of breast cancer.

Overlap: If both pending grants are awarded, only one will be accepted

CONCLUSIONS:

At this point in the research no results are yet available. If results of the proposed research are consistent with the hypothesis that deficits in immune surveillance (eg. as a result of stress) moderate the effects of mutations in primary susceptibility genes the study could have profound implications for the eradication of breast cancer. Such results would raise the possibility that appropriate interventions to reduce stress and increase the activity of immune surveillance mechanisms in women carrying mutations in primary susceptibility genes might delay the onset or prevent the development of breast cancer.